Light-chain nephropathy

A report of 2 cases

K. COOPER, B. C. NATHOO

Summary

Two cases of renal impairment caused by the deposition of monoclonal immunoglobulin light-chain determinants in the glomerular mesangium and basement membranes as well as in the tubular basement membranes of the kidney are described (light-chain nephropathy). Both cases were associated with myeloma. Examinations by light microscopy, immunohistochemistry and electron microscopy are also described. Differential diagnoses on light microscopy include diabetic glomerulosclerosis (Kimmelstiel-Wilson lesions), amyloidosis and mesangiocapillary glomerulonephritis type 1.

Myeloma kidney is characterised by the presence of renal tubular precipitation of abnormal light chains, formation of characteristic casts, and a foreign-body giant-cell reaction to the casts. The term Bence Jones cast nephropathy has also been suggested for these lesions. A further renal abnormality associated with multiple myeloma and plasma cell dyscrasias is light-chain nephropathy (LCN). This form of renal injury encompasses monoclonal immunoglobulin light-chain deposits in the glomerular mesangium and basement membrane as well as in tubular basement membranes.

The first 2 cases of light-chain nephropathy diagnosed at King Edward VIII Hospital, Durban, are reported.

Case reports

Case 1

A 32-year-old woman was referred from a peripheral hospital to King Edward VIII Hospital for investigation of anaemia and renal failure. She had complained of dyspnoea on exertion, swelling of the body and palpitations for 3 months. Physical examination revealed anasarca and marked pallor. The blood pressure was 140/90 mmHg and the pulse 96/min. The jugular venous pressure was elevated to 7 cm and heart sounds were normal. Basal crackles were present on chest auscultation. The full blood count showed a normocytic normochromic anaemia — haemoglobin 3,3 g/dl, white cell count 11,5 x 10^9/l with normal differential count, and platelets 183 x 10^9/l.

The clinical problem of renal failure (serum urea level 35 mmol/l, potassium 4,1 mmol/l and creatinine 830 μmol/l) was managed with peritoneal dialysis. A diagnosis of IgG myeloma was established on a bone-marrow plasmacytosis of 80% and a serum protein electrophoretic monoclonal γ peak, which was identified by immunofixation electrophoretic techniques (IgG paraprotein > 5,2 g/dl).

Lytic lesions were not demonstrated on skeletal survey. The 24-hour urine sample contained 6,09 g protein with a peak in the β region. A positive Bradshaw's test for Bence Jones protein was also demonstrated. Serum creatinine clearance was 6 ml/min.

Ultrasonography revealed both kidneys to be of normal size. Other pertinent blood investigations included: serum calcium 2,36 mmol/l, phosphate 1,58 mmol/l, urate 0,47 μmol/l and an erythrocyte sedimentation rate (ESR) of 175 mm/1st h (Westergren).

Renal biopsy showed 16 glomeruli of which one was totally sclerosed. All other glomeruli showed a diffuse increase in mesangial matrix and cells, with the formation of peripheral mesangial nodules in 5 glomeruli (Fig. 1). These nodules stained positively with periodic acid-Schiff and were partially argyrophilic (Fig. 2). Most of the capillary loops peripheral to mesangium had patent lumina with unremarkable capillary walls. Tubules showed foci of atrophy with thickening and lamination of the basement membrane, accentuated by...
periodic acid-Schiff stain (Fig. 3). Immunoperoxidase showed positive linear staining of glomerular capillary walls and tubular basement membranes for λ light chains and negative staining for κ light chains (Fig. 4).

No features of Bence Jones cast nephropathy were noted. Special stains for amyloid were negative.

Electron microscopy showed finely granular continuous band-like deposits in the glomerular and tubular basement membranes. This λ light-chain nephropathy was characterised by continuous granular deposits in the subendothelial space and in the lamina rareflecta interna of the glomerular basement membrane (Fig. 5). The tubular deposits were found along the external aspect of the tubular basement membrane (Fig. 6). These electron-dense deposits lacked the fibrillar characteristics of amyloidosis.

Fig. 3. Case 1 — thickening and lamination of tubular basement membranes (periodic acid-Schiff x 600).

Fig. 4. Case 1 — linear granular deposits of λ light chain determinants along the glomerular basement membrane (PAP, anti-λ x 300).

Fig. 5. Case 1 — electron micrograph showing finely granular continuous deposits along lamina rara interna of glomerular basement membrane (x 56 000).

Case 2

A 56-year-old woman was admitted to hospital with a 2-day history of vomiting and colicky abdominal pain. Physical examination revealed marked pallor, a blood pressure of 210/110 mmHg and a pulse of 90/min. The aortic component of the second heart sound was loud and grade II fundal changes were present. Blood investigations demonstrated a normocytic normochromic anaemia — haemoglobin 2.7 g/dl, white cell count 11.5 x 10⁹/l, with a normal differential count, and platelets 340 x 10⁹/l. The serum urea level was 15.6 mmol/l and creatinine 252 μmol/l.

A diagnosis of light-chain myeloma was made on marrow plasmacytosis of 18% and a monoclonal γ peak on urine electrophoresis (identified as free κ chains with immunofixation techniques). There was no monoclonal peak on serum electrophoresis or lytic lesions on skeletal survey.

Additional investigations included: 24-hour urine protein 2.24 g, normal-sized kidneys on ultrasonography, serum calcium level 2.05 mmol/l, phosphate 1.27 mmol/l and urate 0.64 mmol/l.

The dominant feature on renal biopsy was benign hypertensive nephrosclerosis. In addition a few glomeruli showed nodular glomerulosclerosis with similar staining properties to case 1 (Fig. 7). Tubular basement membranes were also pronounced and thickened. Immunoperoxidase showed granular positive staining of mesangial nodules (Fig. 8) and linear staining of tubular basement membranes for κ light chains and negative for λ light chains. There were no features of Bence Jones cast nephropathy or amyloidosis.

Pronounced dark band-like finely granular electron-dense deposits on the external aspect of the tubular basement membranes dominated the electron microscopic picture. These deposits were not fibrillar amyloid ultrastructures.

Discussion

The pathological manifestations of multiple myeloma in the kidney include renal amyloidosis, nephrocalcinosis, urate
binding to Congo
glomerular deposits showing

Correct. 

Deposition is not
in the form of an amorphous substance in the
with advanced
al.

is
ubse­

as the most frequent extrarenal complications.

important to note that LCN may also occur with non-myelo­
mature plasma cell dyscrasia.

manifestation of light-chain deposits.

been documented.

The incidence of LCN is underestimated because sera against
light-chain determinants have not been routinely used in the past. Although light-chain deposition disease was first described as a nephropathy, extrarenal manifestations have since been noted. In Ganeval’s experience of 14 patients, extrarenal light-chain deposits were found in all 9 patients in whom they were sought. This study also reported hepatic and cardiac involvement as the most frequent extrarenal complications.

The two cases presented were not investigated for extrarenal manifestation of light-chain deposits.

Whereas both our cases were associated with myeloma, it is important to note that LCN may also occur with non-myoelomatosus plasma cell dyscrasia. Our cases also illustrate that LCN may be induced by either monoclonal \( \gamma \) or \( \lambda \)-chain determinants. This has been confirmed in other series. Thus the previous suggestion that the glomerulopathy associated with monoclonal light chains occurs exclusively as a consequence of \( \gamma \)-rather than \( \lambda \)-chain deposition is not correct. 

Immunohistochemical localisation of the abnormal monoclonal light chain to the basement membrane of tubules, glomerular basement membrane and glomerular mesangium is essential for diagnosis of LCN. Occasionally, light chains have been described in the walls of arteries and arterioles. Also, deposits may be found only along the tubule basement membrane even when glomeruli are clearly abnormal. The reasons for tissue deposition of abnormal light chains are unknown and there is no precise explanation why some patients develop Bence Jones cast nephropathy while others develop light-chain deposition disease. It is also uncommon to observe both these conditions in the same kidney.

The nodular glomerulosclerosis of LCN is similar to the light microscopic abnormalities seen in diabetic glomerulosclerosis (Kimmelstiel-Wilson lesion), renal amyloidosis and mesangiocapillary glomerulonephritis type 1.

Monoclonal immunoglobulin light-chain demonstration with immunohistochemical techniques is essential to distinguish LCN from Kimmelstiel-Wilson lesions of diabetic glomerulosclerosis. It is possible that some of the cases of prediabetic glomerulosclerosis reported in patients without any evidence of overt diabetes mellitus may well have been misdiagnosed cases of LCN.

Renal amyloidosis is distinguished by its binding to Congo red dye and its fibrillar configuration on electron microscopy. It has been suggested that the variation in the structure and physicochemical property of light chains may determine its deposition pattern and structural characteristics.

The extensive mesangial interposition and double contour of glomerular capillary loops (light microscopy), coarse granular C3 along peripheral capillary loops (immunohistochemistry) and electron-dense deposits easily serve to differentiate mesangiocapillary glomerulonephritis from LCN.

Bradley et al. have stated that the diagnosis of LCN is important in order to recognise the presence of an underlying pathological process and thereby direct treatment towards the source of the light-chain production, e.g. chemotherapy as in myeloma.

Ganeval recommends that treatment of this disease should have two aims. Firstly, treatment must improve or stabilise renal failure and, secondly, treatment must try to prevent extrarenal deposition of light chains. He has shown that patients treated in the early stage of the disease stabilised or had improved renal function. In contrast, those with advanced disease developed end-stage renal failure and required haemodialysis.

Both patients in our study received chemotherapy but subsequently died in renal failure.

We thank Miss M. Pillay for typing the manuscript; Dr R. Chetty for reading the manuscript; and Miss Denise Matthias for assistance with electron microscopy.

REFERENCES

Euthyroid hyperthyroxinaemia due to endogenous antibodies to thyroxine and tri-iodothyronine

A case report

G. P. MULLIGAN, J. S. DAVIDSON, H. KAPLAN, M. J. ABRAHAMSON

Summary

A case of euthyroid hyperthyroxinaemia caused by auto-antibodies to thyroxine and tri-iodothyronine is presented. Gel filtration chromatography of the patient's serum showed increased binding of radio-labelled thyroxine analogue to a macromolecular component, which migrated in the gammaglobulin region on electrophoresis. Precipitation by protein A confirmed that this was an immunoglobulin. The importance of recognising this condition so that inappropriate therapy can be avoided is stressed.

Euthyroid hyperthyroxinaemia is an uncommon condition in which thyroid hormone levels are elevated in the absence of thyrotoxicosis. The causes (Table I) include inherited or acquired abnormalities of serum thyroid hormone-binding proteins, auto-antibodies against thyroid hormones, drug effects on thyroid hormone metabolism, and peripheral resistance to thyroid hormones. Recognition of these syndromes is important so that unnecessary and potentially harmful therapy can be avoided. A case in which auto-antibodies to thyroxine (T4) and tri-iodothyronine (T3) caused spurious elevation of serum free T4 (FT4) and free T3 (FT3) levels resulting in an incorrect diagnosis of thyrotoxicosis and subsequent inappropriate therapy is reported.

TABLE I. CAUSES OF EUTHYROID HYPERTHYROXINAEMIA

1. Increased thyroid hormone binding to proteins
   - Thyroid-binding globulin (e.g. pregnancy, oestrogens, inherited)
   - Binding to albumin (familial dysalbuminaemic hyperthyroxinaemia)
   - Thyroxine-binding pre-albumin (inherited)
   - Antithyroid hormone antibodies

2. Tissue resistance to thyroid hormones (sporadic or inherited)

3. Transient hyperthyroxinaemia in acute non-thyroidal and psychiatric illness

4. Drug inhibition of T4 to T3 conversion (iopanoate, iopodate, amiodarone)

Modified from Borst et al.1 and Sakata et al.2

Case report

A 59-year-old woman was seen in January 1987 for routine assessment as she had recently undergone a partial thyroidectomy for removal of a dominant thyroid nodule. Apart from mild obstructive lung disease for which she took oral and inhalational bronchodilator agents there was no other significant past medical history. On direct questioning she denied any symptoms of thyroid dysfunction. Clinical examination revealed no evidence of hyperthyroidism apart from a resting pulse rate of 104/min. The scar from the recent thyroidectomy was noted.

The FT4 and FT3 levels measured by an analogue-based radio-immunoassay (RIA) (Amerlex M; Amersham International, UK) were both elevated at 144 pmol/l (normal 6.3-22.8 pmol/l) and 10.8 pmol/l (normal 3.3-8.1 pmol/l) respectively. She received iodine-131 10 mCi. Three months later the FT4 level was still elevated at 103 pmol/l and the FT3 level was normal (6.7 pmol/l); another 111I 10 mCi was administered. When thyroid function tests performed a further 3